Author's response to reviews

Title: Human Physiologically Based Pharmacokinetic Model for Propofol

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Version: 3 Date: 16 November 2004

Author's response to reviews: see over
Response to Dr. Richard Upton's review of the revised version of "Human Physiologically Based Pharmacokinetic Model for Propofol" by D. G. Levitt and T. W. Schnider.

Major Change:

Dr. Upton's primary criticism concerns the procedure we used for fitting the parameters. In an attempt to meet this criticism, we reanalyzed the data using a "weighted least square" procedure as suggested by Dr. Upton. In the original version we used two adjustable parameters for each subject (the liver clearance and the fraction free in plasma). (For some subjects, two additional parameters were required to describe the pulmonary sequestration). During this reanalysis we realized that the fits were not significantly improved by allowing the fraction free to vary. Thus, in this revised version, all of the subjects are fit using just one value of fraction free (=0.022, the average experimentally reported value) and only adjusting one parameter (the liver clearance) for each subject. We feel that this change definitely increases the significance of this manuscript: Using just one adjustable parameter (the clearance), we can now describe the complete blood concentration time curve (bolus plus constant infusion) with accuracy just slightly worse than the NONMEM compartmental model with 6 adjustable parameters for just the constant infusion phase. In addition, using just one adjustable parameter significantly improves the confidence we can place in the extrapolation of the PBPK model to other physiological conditions.

This change from 2 to 1 adjustable parameter requires minor changes in wording throughout the manuscript and Abstract. In addition, the results shown in figures 5 - 11, 12 and 13 and Tables III and IV required recalculation and revision. The changes are very small.

Detailed response to Dr. Upton's comments (our response is in italics):

1. The model is highly dependent on the presence of variable lung sequestration after a bolus but not an infusion. The authors have quoted the data of He et al. to support this, but I think their analysis falls into a common and long standing misconception with the analysis of dual indicator of lung kinetics. I tried to address this in a review at one point (Upton RN, Doolette DJ. Kinetic aspects of drug disposition in the lungs. Clin Exp Pharmacol Physiol 26: 381-391 (1999)). In brief, this review showed via modelling that the passage of a drug (with a mean transit time of less than 1 min and no sequestration) through the lungs can appear to have a retention (sequestration) of 66% when compared to a vascular indicator. This apparent sequestration is simply artefact to due to the study design. I don't expect the authors to change their point of view, but I think they should actively pursue evidence for this lung sequestration of propofol. My own analysis of Fig. 1 from the He paper via first-pass modelling suggests that only 10% of the propofol dose is unaccounted for.

As we understand the above statement that "I don't expect the authors to change their point of view, but I think they should actively pursue evidence for this lung sequestration of propofol" - the purpose of this comment is to alert us about this
problem, and does not require any modifications of the manuscript. We certainly agree that this issue is not settled and requires further work.

2. The unusual method used for curve-fitting remains unjustified and unreferenced. The authors claim that the "weighted residual method" is a common statistical technique for fitting data, particularly in X-ray crystallography. However, when the phrase "weighted residual method" is entered into Google, only 5 hits are returned. When "weighted least squares" is entered, there are 35,900 hits. If something other than "weighted least squares" is used for curve-fitting, it needs to be justified and referenced.

As described above ("Major Change") we have now completely revised the curve fitting procedure and now use a "weighted least squares" procedure as requested (described in detail in Methods).

3. The lack of standard errors for the parameter estimates, and correlation between the parameters values, means that the model building process falls short of accepted modelling practice. It is possible to achieve good fits of data with parameter values that are highly correlated or undetermined (that is, they are not a unique solution to the problem). I find it strange that the authors have avoided using the standard least squares curve-fitting routines in Maple that could easily return these values via a Hessian matrix, but went for their poorly documented "weighted residual method".

This is similar to criticism #2 above. At stated, we have recalculated all the individual fits using a least squares procedure. Since, in this new version, only 1 parameter is varied during the fitting procedure, this should eliminate the reviewer's concern about "...achieving good fits of data with parameter values that are highly correlated or undetermined (that is, they are not a unique solution to the problem)"